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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,868	11/17/2003	Juan Arroyo	06132/075002	5599

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EXAMINER	
SALVOZA, M FRANCO G	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 09/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,868	ARROYO ET AL.	
	Examiner	Art Unit	
	M. Franco Salvoza	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/3/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The application claims priority under 35 U.S.C. 120 to provisional application 60/426,592 dated November 15, 2002.

2. Claims 1-14 are pending and under consideration.

Specification

The disclosure is objected to because of the following informalities: it needs the application number on the first page. Appropriate correction is required.

The abstract of the disclosure is objected to because the application number is missing. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim states "wherein said pre-membrane or envelope protein comprises an attenuating mutation," indicating through "an" a single mutation, but it is not clear in which protein the attenuating mutation is found or whether it is found in either one.

Claims 6-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The word "thereof" does not make it clear whether "conservative amino acid

thereof" refers to the first or second named amino acid.

Claim 14 provides for the use of the chimeric flavivirus of claim 9 in vaccination against West Nile virus, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 14 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a chimeric virus comprising an attenuated Yellow Fever virus backbone encoding a West Nile pre-membrane and envelope proteins comprising multiple locations or single locations at position 107, does not reasonably provide enablement for a single site attenuated mutation as recited in claim 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. Claim 1 describes an attenuated mutation, for which limitations are added at positions 107, 316 and 440.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

> The breadth of the claims: The claim to "an attenuating mutation" is too broad for the amount of evidence presented, claiming an attenuating mutation when the evidence presented is limited to a sample of mice and monkeys and further, that a single mutation as recited in claims 1 and 3 is not enough to achieve the proper level of attenuation.
>
> This is further illustrated by Arroyo et. al. in "ChimeriVax-West Nile Virus Live-Attenuated Vaccine: Preclinical Evaluation of Safety, Immunogenicity and Efficacy." (2004, Journal of Virology Vol. 78, No. 22:12497-12507). Arroyo illustrates the importance of multisite mutations or a combination of them rather than a single mutation in order to attain a properly attenuated mutation. On p. 12500, Arroyo states, "Neurovirulence of the YF/WN chimeras in which modified amino acids were inserted in the E protein at residues 107, 316, and 440 were the most important contributors to neurovirulence."
>
> The state of the prior art: A search of the prior art shows a reasonable amount of success for chimeric vaccines combining the Yellow Fever backbone with other flaviviruses, yet the added novelty of the attenuated mutation or combination of these particular mutations and the broad scope claimed therefrom is not enabled given the evidence presented.

The existence of working examples: Applicant provides results from studies using a sample of mice and monkeys, some of which started to exhibit virulence post challenge. However, these mice and monkeys are examples of a common host for viral studies and fail to show a proper nexus between the results in these hosts and a human subject to satisfy the scope claimed.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: Proper use of the invention would require added undue experimentation using the attenuated mutation or combination of attenuated mutations to be successful for the scope claimed.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement).

Therefore, claims 1-14 are rejected under 35 U.S.C. 112, 1st paragraph for scope of enablement, since the claims recited are overbroad for the evidence presented.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8 and 9 of U.S. Patent No. 6, 878, 372 to Monath et al. Although the conflicting claims are not identical, they are not patentably distinct from each other because U.S. Patent No. 6, 878, 372 claims a method of preventing or treating West Nile virus infection, said method comprising administering a chimeric flavivirus comprising the capsid and non-structural proteins of a yellow fever virus and the pre-membrane and envelope West Nile virus. Applicant's claim 10 is rendered obvious under claim 1 of the Monath reference, since in both instances the chimeric flavivirus would be used in a method to induce an immune response to West Nile Virus in a subject.

Further, applicant claims in claim 11 that the subject is at risk of developing West Nile virus infection, which is obvious over Monath's claims 1 and 8, which recite a method of preventing West Nile virus infection in a subject that does not have it but is at risk of developing it. Finally, applicant's claim 12 is obvious over Monath's claims 1 and 9 drawn to the method of treating a subject already infected by West Nile virus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 9-13 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent #6,696,281 to Chambers et. al. The Chambers patent has a filing date of Dec. 1, 1999 and an issue date of Feb. 24, 2004.

Claim 1 is drawn to a nucleic acid molecule comprising sequences encoding the pre-membrane and envelope proteins of West Nile virus and the capsid and non-structural proteins of Yellow Fever virus, wherein the pre-membrane or envelope protein comprises an attenuating mutation. In column 6, lines 36 – 67 and column 7, lines 27-59, the Chambers patent teaches a chimeric virus combining a Yellow Fever backbone with a capsid and non-structural proteins with the pre-membrane and envelope proteins of another flavivirus, such as West Nile. Furthermore, in column 3, lines 62-63, the Chambers patent states that included in the invention are nucleic acid molecules encoding the chimeric flaviviruses, administration, use and methods of manufacturing them to anticipate claims 9, 13 and 14.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guirakoo et al. ("Immunogenicity, Genetic Stability, and Protective Efficacy of a Recombinant, Chimeric Yellow Fever-Japanese Encephalitis Virus (ChimerVax-JE) as a Live, Attenuated Vaccine Candidate against Japanese Encephalitis"; Virology 257, 363-372 (1999)), Poidinger et al., ("Molecular Characterization of the Japanese encephalitis serocomplex of the flavivirus genus"; Virology 218:417-421 (1996)), Yang et al., ("Induction of Potent Th1-Type Immune Responses from a Novel DNA Vaccine for West Nile Virus New York Isolate (WNV-NY1999); The Journal of Infectious Diseases 184:809-16 (2001)), and Allison et al. ("Mutational Evidence for an Internal Fusion Peptide in Flavivirus Envelope Protein E" Journal of Virology, May 2001; p. 4268-4275).

Guirakoo teaches that the Yellow Fever virus can be used as a backbone to deliver genes for flaviviruses, such as the combination of the YF 17D and pr-ME genes of Japanese Encephalitis Virus. Poidinger teaches that Japanese Encephalitis is a close genetic relative of West Nile. Yang teaches that West Nile virus antigens can be used to induce an immune response. Finally, Allison teaches the introduction of amino acid substitutions in flavivirus envelope protein E at position 107 to Leucine has the attenuating property of inhibiting fusion without disruption of native structure.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the Yellow Fever backbone of Guirakoo and West Nile envelope proteins of Yang in light of Poidinger to create a chimeric flavivirus to induce an immune response to West Nile. One of ordinary skill, in the art at the time the invention was made would have had a further motivation to attenuate at specific positions such as 107 on the flavivirus envelope

protein because Allison teaches that this mutation has attenuating properties.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for success in combining West Nile and Yellow Fever backbone since Guirakoo teaches that flaviviruses such as Japanese Encephalitis can be delivered on a Yellow Fever backbone and Poidinger teaches that Japanese Encephalitis is a close genetic relative of West Nile. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to M. Franco Salvoza whose telephone number is (571) 272-8410. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

M. Franco Salvoza
Patent Examiner

SHANON FOLEY
PRIMARY EXAMINER